EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Compliance and Inspection

Concept paper on the need for a single note for guidance on the chemistry of active substances

Agreed by Quality Working Party	December 2013
Adopted by CHMP for release for consultation	19 December 2013
Start of public consultation	10 February 2014
End of consultation (deadline for comments)	10 August 2014

The proposed guideline will replace the “Note for guidance on chemistry of new active substances” (CPMP/QWP/130/96, Rev 1) and “Chemistry of active substances” (3AQ5a)

Comments should be provided using this template. The completed comments form should be sent to QWP@ema.europa.eu

Keywords	Guideline, Chemistry, Drug substance, Active substance

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1. Introduction

This concept paper addresses the need to update and revise the guidance available on the chemistry of the active substance. There are currently two approved guidelines on the subject; CPMP/QWP/130/96, Rev1 Note for guidance on the chemistry of new active substances and 3AQ5a, chemistry of the active substance. The former guideline was originally adopted in December 2003 and came into operation in February 2004 whilst the latter was adopted in October 1987 (which is over 25 years ago). It is felt appropriate to combine the two documents into a single guideline to provide better clarity for applicants. Additionally, since these documents were approved, there have been many changes in the regulatory requirements for example, introduction of the common technical document (CTD), changes to references to directives and guidelines and publication and approval of new guidance documents (e.g. ICH Q11, guideline on the limits of genotoxic impurities CPMP/SWP/5199/02, and guideline on the specification limits for residues of metal catalysts or metal reagents CPMP/SWP/QWP/4446/00 etc.).

The guidance documents therefore need to be combined and revised to be in line with all these changes and to facilitate the understanding of the applicant regarding the information required.

2. Problem statement

The current guidelines do not fully reflect recent development and changes both in legislation and available guidance documents as well as nomenclature. The guideline should be clarified in certain places.

3. Discussion (on the problem statement)

The following issues will be taken into account during revision:

The combined guideline will follow the structure of the CTD (as does the CPMP/QWP/130/96, Rev1 Note for guidance on the chemistry of new active substances).

The ICH guideline Q11 on development and manufacture of drug substances should be reflected in this guideline and therefore the information in the guideline will be updated accordingly.

It will be clarified that this guideline is applicable to applications which follow the “traditional” approach and not the enhanced approach which is also included in the ICH guideline Q11 on development and manufacture of drug substances.

Further clarification on the principles and concepts described in ICH guidelines on pharmaceutical development (Q8), quality risk management (Q9) and Pharmaceutical Quality System (Q10) as they pertain to the development and manufacture of active substances should be introduced where appropriate.

It is important to outline that it is not intended to revise the Note for guidance on the chemistry of new active substances in a way to reduce or replace the level of detail of the current guidelines which is of major significance.

The presence of genotoxic impurities in active substances is a critical issue with respect to safety and is currently not reflected appropriately in the existing guidelines.

Editorial changes and minor clarification of the current wording are necessary.

4. Recommendation

The Quality Working Party (QWP) recommends the elaboration of a single guidance document on the chemistry of the active substance which will replace the existing approved guidelines on the subject; CPMP/QWP/130/96, Rev1 Note for guidance on the chemistry of new active substances and 3AQ5a, chemistry of the active substance. This revision will clarify the requirements for all applications regarding active substances and will bring the guidance in line with recent development and the current EU legislation.

5. Proposed timetable

December 2013 - Discussion on concept paper in QWP.

It is anticipated that the draft guideline could be available 6 months after adoption of the concept paper and that this would then be released for external consultation for 6 months before its finalisation within another 6 months.

It is expected that the guideline will come into operation six months after adoption.

6. Resource requirements for preparation

The revision will involve the EMA-QWP Secretariat, the Joint CHMP/CVMP Quality Working Party, the CHMP, and GMP/GDP Inspectors Working Group, who would be consulted, as necessary. The QWP should appoint rapporteur and drafting group from the members of QWP.

7. Impact assessment (anticipated)

No adverse impact on industry with respect to either resources or costs is foreseen.

The revised guideline will not introduce new requirements on medicinal products already authorised and on the market.

The guidance will clarify requirements for regulators and industry with respect to the chemistry of active substances taking into account the concepts of recent development.

8. Interested parties

Pharmaceutical industry, EU competent authorities, GMP/GDP Inspectors Working Group

9. References to literature, guidelines, etc.

1. ICH guideline Q11 on development and manufacture of drug substances (chemical entities and biotechnological / biological entities) CHMP/ICH/425213/2011 (ICH Q11).
2. Active substance-master-file procedure CHMP/QWP/227/02.
3. Summary of requirements for active substances in the quality part of the dossier CHMP/QWP/297/97.
4. Chemistry of active substances 3AQ5A.
5. Test procedures and acceptance criteria for new drug substances and new drug products: chemical substances Q 6A specifications CPMP/ICH/ 367/96 (ICH Q6A).
6. Impurities testing: impurities in new drug substances CPMP/ICH/2737/99 (ICH Q3A).
7. Impurities: residual solvents CHMP/ICH/82260/2006 (ICH Q3C).

8. Specification limits for residues of metal catalysts CPMP/SWP/QWP/4446/00.
9. Limits of genotoxic impurities EMEA/CHMP/QWP/251344/2006.
10. Setting specifications for related impurities in antibiotics CHMP/CVMP/QWP/199250.
11. Validation of analytical procedures: text and methodology CPMP/ICH/381/95 – (ICH Q2).
12. Plastic primary packaging materials CPMP/QWP/4359/03.
13. Stability testing of new drug substances and drug products CPMP/ICH/2736/99-ICH (ICH Q1A).
14. Photo stability testing of new active substances and medicinal products CPMP/ICH/279/95-ICH (ICH Q1B).
15. Evaluation of stability data CPMP/ICH/420/02-ICH (ICH Q1E).
16. Stability testing for applications for variations to a marketing authorisation EMA/CHMP/CVMP/QWP/63033/2010.
17. Quality of water for pharmaceutical use CMPM/QWP/158/01.
18. Investigation of chiral active substances III/3501/91.